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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,288	08/20/2003	Paul Diamond	PT100-3	5798

7590 08/29/2006

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 08/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/644,288	DIAMOND, PAUL	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *1-16,21,23,28,31 and 33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20, 22, 24, 25, 27, 29, 30, 32, and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 18, 20, and 29 have been amended. No new matter was introduced by these amendments. Claims 1-16, 21, 23, ~~16~~ 26, 28, 31, and 33-35 have been withdrawn. J.E. 8-21-06

Claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 101

3. The rejection of claims 18-20, 22, 29, 30, and 32 under 35 USC § 101 for being directed to non-statutory subject matter is withdrawn in response to Applicant's amendments to the claims filed on 06/13/2006.

Claim Rejections - 35 USC § 112 - enablement

4. Claims 25, 27, 29-31, and 36 remain rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement for the reasons of record set forth in the prior Office Action.

Applicant's arguments filed on 06/13/2006 have been fully considered but they are not persuasive. Applicant traversed the instant rejection on the grounds that the Examiner's reliance on Kolb et al. is improper because (i) Kolb et al. teach novel and developing strategies in the field of gene targeting and not the random integration or

homologous recombination that are commonplace within the art and therefore their review focuses on strategies to engineer enzymes with novel DNA targeting abilities; for these reasons Applicant concludes that the teachings of Kolb. et al. apply only to new enzymes engineering strategies and not to the random integration or homologous recombination methods, (ii) Kolb et al. teach gene-targeted integration for gene therapy and animal transgenesis, whereas the instant claims are not directed to gene repair or gene therapy, which both require high efficiencies in many cells to correct some deficiencies in a preexisting organism. Applicant asserts high efficiency is not required for enablement, since selection schemes are routinely used in the art to produce genetically modified cells and organisms. Moreover, Applicant argues, the Examiner's reliance on Coates et al. and Wurtele et al. is improper because Coates et al. are biased and stress only the alleged shortcomings in the presently used methods and the citations from Wurtele et al. were taken out of context. As a consequence, even if the Coates et al. teach that integration at random sites often places the transgene into an environment that is not supportive of its expression and even if Wurtele discusses problems that may be caused by illegitimate DNA integration, the well established selection schemes known in the art can be used to obtain genetically modified cells expressing to the desired extent. With respect to Vasquez reference, Applicant asserts that enablement does not require the task be easy, it is enough for enablement that gene targeting is a standard tool that requires persistence because, with persistence, there is a reasonable expectation of success. With respect to Iida et al., Applicant argues that Iida itself contradicts the Examiner's assertion, because the cited passage

does not take into the account the work of Iida, which shows that the prior Waxy gene work of Tekada et al. (2002) is generally applicable to other genes (p. 213) and therefore the instant invention was enabled at the time of filing. With respect to Examiner's assertion that inhibiting a gene encoding for a transcriptional repressor might not work because transcription is carried out by assemblies of transcription factors and many of them are redundant in the cell, Applicant argues that it is not necessary for all embodiments to always work to be enabled, as long as one of skill in the art could determine, without undue experimentation, which embodiments would be inoperative or operative. Moreover, if it is necessary to eliminate the function of two or more redundant transcription factors to affect transcription, this can be readily determined by using commercially available anti-sense or RNA-silencing reagents. Applicant continues arguing that the enablement does not require that the subject task be easy and the mere fact that gene targeting is a standard tool that requires persistence is enough for one of skill in the art to have a reasonable expectation of success. Therefore what is required for enablement is that one of skill in the art engaging in experimentation typical of the art can practice the invention. With respect to Sledz reference and RNAi resistance, the Applicant asserts that these bases of rejections are not applicable because gene therapy is not claimed and therefore, the delivery concerns specific to therapy are not an issue and non-specific effects do not necessarily pose any problem with the claimed inventions so long as the desired target is silenced. With respect to Woessmann reference, Applicant argues that the citation teaches cancer gene therapy and, since the present invention does not relate to the

treatment of tumors, the context of treating a tumor with RNAi is not applicable to the present claims. With respect to the antagonism of RNAi by the RNA editing process, this is not a problem for the presently claimed invention because the claimed cells are genetically engineered to comprise specific DNA sequences, and therefore any hypothetical concern can be addressed by modifying a gene to eliminate or change the RNA editing, for example to construct and use a mini-gene that does not contain introns, as opposed to using the gene that contains itself. With respect to Opalinska, the Applicant argues that the reference is a review of nucleic acid-based therapy in general, and is not specific to RNA silencing approach and therefore is questionable and should not be relied upon. Applicant concludes that the cited references support the enablement of the instant invention and therefore the Applicant requests the withdrawal of the rejection.

Contrary to Applicant's assertions, the cited references do not enable the instant invention for the reasons stated in the prior Office Action. First, the teachings of Kolb et al. are not limited to new enzyme engineering strategies; they clearly teach gene therapy (i.e., modulation of gene expression) and problems associated with it. Although Kolb et al. do not teach modulation of gene expression by random integration, they certainly do teach homologous recombination (p.399, column 2, second paragraph. 400, column 2, second paragraph). Kolb et al. teach enzyme engineering only as a strategy to overcome problems associated with modulation of gene expression by homologous recombination (p. 400, column 2 bridging p. 401). Therefore, the teachings of Kolb et al. do apply to homologous recombination. Kolb et al. teach that modulating

gene expression by using a particular methodology might work well for some cells but not for others and that there are many other problems that need to be overcome (p. 405, Conclusion). Applicant's assertion that the instant invention does not require high efficiency for enablement is not found persuasive. Even if selection schemes were available, due to the very low efficiency, one of skill in the art would not be able to practice the claimed invention without undue experimentation or to be able to predict that the selection schemes would work. For example Vasquez et al. clearly teach that the principal barrier in gene targeting is the high frequency of random (non-homologous) integration that obscure the inefficient targeted integrations (see p. 11 of the previous Office Action. With respect to the inefficient targeted integration and the selection process, Kolb et al. teach:

> "Homologous recombination between the exogenous and chromosomal DNA is typically highly inefficient, perhaps 10^{-6} correct events per genome. For mouse embryonic stem cells, the poor frequency of recombination has been ameliorated by the development of excellent screening procedures. However, extension of these methods to other cell types remains elusive."

Therefore, one of skill in the art would not reasonably predict that the instant methodology could be used to modulate gene expression in any cell or organism, as claimed.

Second, the basis for Applicant's assertion that the teachings of Coates et al. are biased in showing the shortcomings of the presently used methods is unclear. Although Coates et al. teach six different integration systems that are used in laboratories (p. 416, Table 2) and several problems associated with them, they also teach that improving the efficiency of these systems, although not yet achieved, is a technical possibility (p. 416, columns 1 and 2, p.417, columns 1 and 2). With respect to Wurtele et al., they clearly

teach that, although integration of foreign DNA is widely used in molecular biology, problems with illegitimate integration still remain and many aspects of the illegitimate integration require further investigation to control this undesired event (Abstract, p. 1792, column 2, p. 1796, *Conclusions and Perspectives*). With respect to the argument of overcoming these problems by selection, see above.

Third, while Iida et al. teach that the work of Tekada et al. is applicable to other genes in rice, they do not teach other plants or other organism and they do teach that even in rice the progress is not so fast and there is a need for more scientific research to improve the procedure p. 216, column 1, *Conclusions*). Therefore, the work of Iida does not enable Applicant's invention that claims genetic modification of any cell in any organism.

Fourth, the argument that one of skill in the art could determine, without undue experimentation, whether the expression of a gene can be manipulated by inhibiting one of its transcriptional repressors is not found persuasive for the reasons set forth in the prior Office Action. Applicant argues that if it is necessary to eliminate the function of redundant transcription factors, this can be readily achieved by using the commercially available anti-sense and RNA-silencing reagents. To achieve this, one of skill in the art would have to first determine how the transcription machinery assembles to the gene of interest, the transcription factors that are part of that machinery, and which transcription factors are redundant. It is noted that this is not routine experimentation. Since these data are known only for a few genes, one of skill in the art would require undue

experimentation to accumulate the necessary knowledge to practice the invention with any gene, in any cell or organism.

Fifth, the argument that Sledz's teachings do no apply to the instant invention because the delivery concerns are specfic for gene therapy only and not for random or homologous recombination is not found persuasive because delivery concerns and non-specific effects still apply if the invention is practiced with a living organism. The claim language discloses "providing a cell comprising a series of DNA sequences " or "a cell not integrated with a human being". Such language encompasses cells *in vitro*, *ex vivo* or *in vivo* and therefore delivery is still a problem if the claimed invention is to be practiced in an organism.

Sixth, with respect to Woessmann, while it is true that the citation mentions cancer gene therapy, the main teaching is that even minor alterations in the sequence of the gene targeted by RNAi could antagonize RNAi. The assertion that the RNA editing process can be overcome by using a mini-gene that does not contain introns is not found persuasive because the RNA editing machinery alters mRNA sequences after transcription from the genomic template, therefore the mini-gene can still be subjected to the editing process.

Seventh, with respect to Opalinska, it is not clear why the reference is questionable, since consideration that apply to nucleic acids, in particular anti-sense oligonucleotide also apply, since siRNA mediate the silencing of target mRNAs.

For these reasons and for the reasons set forth in the prior Office Action, it is concluded that claims 17-20, 22, 24, 25, 27, 29, 30, 32, and 36 are not enabled.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER